

## **REMARKS**

The Applicants have carefully considered this application in connection with the Examiner's Action and respectfully request reconsideration of this application in view of the foregoing amendment and the following remarks.

The Applicants originally submitted Claims 1-36 in the application. In response to the prior office action mailed July 14, 2003, the Applicants made an election of species to facilitate the Examiner's review for potential prior art. In response to the present office action, the Applicants have amended Claims 1-4, 10-11, 16, 24 and 34-36. Claims 1, 10 and 24 now include elements that were previously recited in Claim 2-3, 11 and 34-35. Support for the amends to Claim 2, 4, 11 and 34-36 can be found in Experiments 1-3, 5 and 14 of the Specification. Support for the amendment to Claim 3 is from paragraph [0050] and Claim 16.

Regarding the Examiner's withdrawal of Claims 15 and 19-22, the Applicants wish to note for the record, that a generic claim, Claim 10, covers these claims. Moreover, if such a generic claim is allowed, then the claims that the Examiner has withdrawn should also be allowable. Accordingly, Claims 1-36 are currently pending in the application.

### **I. Objections.**

The Examiner objected to paragraph [0001]. In response, paragraph [0001] has been replaced with the sentence suggested by the Examiner. In addition, a typographical error in paragraph [0061] has been corrected.

### **II. Rejections of Claims 1-14, 16-18 and 23-36 Under 35 U.S.C. §112 Second Paragraph**

The Examiner has rejected Claims 1-14, 16-18 and 23-36 under 35 U.S.C. §112, first paragraph, for failing to particularly point out and distinctly claim the subject matter that the Applicants regard as the invention. Specifically, the Examiner asserts that the term "R1 includes organic substituents," in Claim 1 uses improper Markush terminology. For the same reason, the

Examiner also objects to the use of open terms such as “including” or “comprising,” in the context of Markush practice in other claims.

In response, the Applicants respectfully submit that there is nothing indefinite in designating R1 as including organic substituents because Claim 1 does not recite a Markush group. This argument also applies to the use of the term “comprising organic substituents” in Claims 10, 15 and 24. In instances where the Applicants intended to recite Markush groups, such as Claim 5, they have indeed used proper terminology. The Applicants therefore see no basis to amend Claims 1-14, 16-18 and 23-36 on the grounds cited by the Examiner.

The Examiner also rejected Claim 16 on the grounds that it is confusing in that it appears to depend on Claim 15, and not Claim 14 as recited. In response, the Applicants have amended Claim 16 to recite dependence on Claim 15.

Therefore, the Applicants and respectfully request that the 35 U.S.C. §112 second paragraph rejections of Claims 1-14, 16-18 and 23-36 be withdrawn.

### **III. Rejection of Claims 1, 5, 8 and 9 under 35 U.S.C. §102(b)**

The Examiner has rejected Claims 1, 5, 8 and 9 under 35 U.S.C. §102(b) as being anticipated by Aime *et al.*, Chem. Commun., 1999, 1047-48 (“Aime”). The Applicants respectfully disagree.

Aime investigated the pH dependence of the luminescence of a Eu-L<sup>3a</sup> complex and the <sup>1</sup>H relaxivity of a Gd-L<sup>3a</sup> complexes as a function of pH and in the presence and absence of hydrogen carbonate, where L<sup>3a</sup> is a  $\beta$ -alanine-analogue-tetra-substituted tetraazacyclododecane, (page 1047, column 1). Aime reports <sup>17</sup>O NMR linewidth experiments done on Gd-L<sup>3a</sup>, indicating that the mean life time for water exchange ( $\tau_m$ ) equals 19.0  $\mu$ s (page 1047, column 2). Aime also did <sup>1</sup>H NMR measurements of the longitudinal relaxation time ( $T_{1m}$ ) of the Gd-coordinated water molecule as a function of pH as part of the <sup>1</sup>H NMR relaxivity study.

In contrast, amended Claim 1 recites that the water molecule associated with the

tetraazacyclododecane ligand and the paramagnetic metal ion has a  $\Delta\omega \bullet \tau_M \geq 1$  and a  $\Delta\omega \geq 6$  ppm. As acknowledged by the Examiner, Aime fails to teach that  $\Delta\omega \bullet \tau_M \geq 1$  and that  $\Delta\omega \geq 6$ . Therefore, Aime does not disclose each and every element of the claimed invention, and as such, is not an anticipating reference. Because Claims 5, 8 and 9 are dependent upon Claim 1, Aime also cannot be an anticipating reference for these Claims.

Accordingly, the Applicants respectfully request the Examiner to withdraw the §102(b) rejections with respect to Claims 1, 5, 8 and 9.

#### **IV. Rejection of Claims 1-18 and 21-22 under 35 U.S.C. §103**

The Examiner has rejected Claims 1-4, 6-7, 10-14, 16-18 and 23-36 under 35 U.S.C. §103(a) as being unpatentable over Aime in view of Ward *et al.*, Journal of Magnetic Resonance, March 2000, 143, 79-87 (“Ward”) and Dunard *et al.* J. Am. Chem. Soc., February 2000, 122, 1506-12 (“Dunard”).

The Applicants respectfully maintain that the claimed invention is not obvious in view of the foregoing combined references, and that this combination fails to establish a *prima facie* case of obviousness of Claims 1-4, 6-7, 10-14, 16-18 and 23-36.

The combination of Aime in view of Ward and Dunard, for instance, fail to teach or suggest all of the elements of the invention recited in independent Claim 1.

As noted above, Aime discloses Eu and Gd complexes of  $L^{3a}$ . There is no recognition by Aime, however, that such complexes could be suitable as CEST contrast agents, as taught in the present invention. For instance, there is no teaching or suggestion by Aime that a bound water molecule associated with either of  $Eu-L^{3a}$  or  $Gd-L^{3a}$  has a  $\Delta\omega \bullet \tau_M \geq 1$  and a  $\Delta\omega \geq 6$  ppm. Aime did not report any NMR properties for  $Eu-L^{3a}$ . Rather, Aime only looked at the luminescence of this complex as a function of pH (pp. 1048; column 1). Aime did perform water  $^{17}O$  NMR line width, and  $^1H$  NMR  $T_{1m}$  measurements, of  $Gd-L^{3a}$  as a function of pH. However, Aime provides no teaching or suggestion that a  $^1H$  NMR signal of a water molecule associate with  $Gd-L^{3a}$  is

visible and distinguishable from that of bulk water.

The Examiner also states that because the contrast agents of Aime have  $\tau_M \geq 1$ , it is obvious that  $\Delta\omega \bullet \tau_M \geq 1$ . The Applicants wish to point out, as noted above, Aime only studied Gd-ligand complexes by NMR. In addition, the Applicants respectfully point out that  $\Delta\omega \bullet \tau_M$  is the product of two terms:  $\Delta\omega$  and  $\tau_M$ . Specifying the value of  $\tau_M$  gives no information on the value of the product  $\Delta\omega \bullet \tau_M$  and there is no teaching or suggestion about the value of  $\Delta\omega$  for Gd- $L^{3a}$ , or any other complex studied by Aime. As demonstrated by the experimental results presented in the Specification of the present application,  $\Delta\omega$  and  $\tau_M$  can vary over a broad range of values, depending on structure of the pendant arms of the ligand and the identity of the metal ion. Moreover the Applicants submit that Gd- $L^{3a}$  is a poor candidate for a CEST contrast agent. As pointed out in the Specification of the present application, contrast agents using metal ions such as  $Gd^{3+}$  shorten  $T_{1sat}$  and therefore are unsuitable at producing MT-based contrast (Experiment 12). Therefore, Aime's showing that certain Gd-ligand complexes have a have  $\tau_M \geq 1$ , does not make it obvious that  $\Delta\omega \bullet \tau_M \geq 1$ .

The Examiner cites Ward for the proposition of teachings that  $\Delta\omega \bullet \tau_M \geq 1$  designates a slow to intermediate exchange rate and that a  $\Delta\omega > 2$  ppm is desirable to avoid direct irradiation of water. The Examiner reasons that it would be obvious to generate a contrast agent where  $\Delta\omega \bullet \tau_M \geq 1$  because Ward discloses a new class of contrast agents based on CEST, where the agents have a slow to intermediate exchange rate governed by the above formula. The Applicants disagree.

Ward's new class of contrast agents are selected intrinsic metabolites, such as amino acids, sugars etc ... (abstract). Contrary to the Examiner's assertion that all of the references are directed to DOTA-lanthanide complexes, Ward specifically rejects metal-based contrast agents because of several perceived drawbacks (pp. 79). As such, Ward does not teach or suggest that metal-ligand complexes could be used as CEST contrast agents. More specifically, Ward gives no indication as to what structure a metal-ligand complex should have to serve as a CEST contrast agent. For instance, Ward offers no indication as to how to increase  $\Delta\omega \geq 6$  ppm. The

Applicants therefore maintain that there is nothing in Ward that teaches or suggests a water molecule associated with paramagnetic metal ion-tetraazacyclododecane ligands, of the structure recited in Claim 1, can have a  $\Delta\omega \cdot \tau_M \geq 1$  and a  $\Delta\omega \geq 6$  ppm.

Dunard is cited by the Examiner to support the argument that it would be obvious to use various lanthanide metals in DOTA-like chelates, because the overall properties of the contrast agent are not drastically altered by metal substitution, and because Dunard allegedly evaluated CEST in such chelates. Again, the Applicants respectfully disagree.

First, the Applicants take issue with the Examiner's assertion that Dunard evaluated CEST in DOTA-like chelates. Rather, Dunard is concerned with understanding the mechanism of water exchange in conventional Gd-based contrast agents in order to design new Gd-based contrast agents (pp. 1506; column 2). To this end, Dunard examines  $^1\text{H}$  and  $^{17}\text{O}$  NMR linewidths of bound water for  $[\text{Eu}(\text{DOTAM})(\text{H}_2\text{O})]^{3+}$  as a function of temperature and pressure (pp. 1508; column 1). The reason why Dunard investigates  $[\text{Eu}(\text{DOTAM})(\text{H}_2\text{O})]^{3+}$  is because the bound water NMR signal of  $[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^-$  is not observable (pp. 1507; column 1). Dunard does magnetization transfer experiments on  $[\text{Eu}(\text{DOTAM})(\text{H}_2\text{O})]^{3+}$ , but these experiments examine the  $^1\text{H}$  NMR signal of cycle protons as a function of ring inversion or arm rotation (FIGURE 5 and pp. 1509; column 2). Dunard, therefore, does not teach or suggest that  $[\text{Eu}(\text{DOTAM})(\text{H}_2\text{O})]^{3+}$ , or any other DOTA-like chelate, can serve as a CEST contrast agent.

Second, contrary to the Examiner's assertion, Dunard demonstrates that the choice of metal and the ligand's structure can quite dramatically alter the overall properties of the metal-ligand-water complexes. For instance, Dunard notes that while La and  $\text{Ce}^{7+}$  complexes of  $[\text{Ln}(\text{DOTA})(\text{H}_2\text{O})]^-$  adopt a m-type structure, other lanthanides adopt an M-type structure (pp. 1506; column 2). Dunard also notes that whereas the NMR signal of bound water in  $[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^-$  is not observable, the NMR signal is visible for  $[\text{Eu}(\text{DOTAM})(\text{H}_2\text{O})]^{3+}$ . These observations suggest that it is not obvious what structural and physical attributes a DOTA-like chelate should have to be a CEST contrast agent.

In summary, because the combination of Aime in view of Ward and Dunard fails to teach

or suggest all of the elements of the inventions of Claim 1, the Examiner cannot establish a *prima facie* case of obviousness of dependent Claims 2-9, which includes all the elements of the independent claims. Analogous arguments apply to independent Claims 10 and 24, and their respective dependent claims.

In addition, the Applicants respectfully submit that the asserted combination of Aime in view of Ward and Dunard fails to establish a *prima facie* case of obviousness because the asserted combination is improper.

The Examiner states that both Dunard and Ward disclose the evaluation of CEST in various compounds. The Examiner also states that all of the references are directed to DOTA-lanthanide complexes and therefore are considered to be in the same field of endeavor. However, as pointed out above, CEST was not evaluated in the compounds studied by Aime or Dunard. Additionally, Ward rejects the use of metal-based contrast agents, because of several perceived drawbacks including toxicity,  $T_2^*$  effects and slow clearance once the contrast agent is administered (pp. 79).

The combination of Ward with either of Aime and Dunard is therefore improper because a person having ordinary skill in the art would not be motivated to find or add to Aime or Dunard the teachings and suggestions of Ward, inasmuch as Ward rejects the use of metal-based contrast agents. Moreover, the combination of Ward with Dunard is improper because while Ward assesses intrinsic metabolites that could serve as CEST contrast agents, Dunard is directed to understanding the structure, rate and mechanism of water exchange in order to design new Gd-based MRI contrast agents. Similarly, the combination of Ward with Aime is improper because Aime is concerned with determining the pH dependence of the luminescence and the  $^1\text{H}$  relaxivity of Eu- and Gd-ligand complexes as a function of pH and in the presence and absence of hydrogen carbonate, not assessing CEST contrast agents.

In view of the foregoing remarks, the cited references do not support the Examiner's rejection of Claims 1-4, 6-7, 10-14, 16-18 and 23-36 under 35 U.S.C. §103(a). The Applicants therefore respectfully request the Examiner to withdraw the rejection.

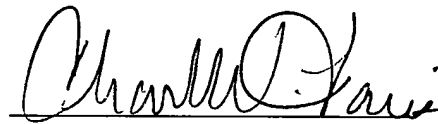
**V. Conclusion**

In view of the foregoing amendments and remarks, the Applicants now see all of the Claims currently pending in this application to be in condition for allowance and therefore earnestly solicit timely a Notice of Allowance for Claims 1-36.

The Applicants request the Examiner to telephone the undersigned attorney of record at (972) 480-8800 if such would further or expedite the prosecution of the present application.

Respectfully submitted,

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Dated: 2/19/04

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